REMARKS

These remarks are in response to the Office Action mailed June 19, 2007. Claims 31-33 and 37 have been amended to address grammatical/formalities errors. Claims 39-41 have been added.

The specification has been amended to overcome the Examiner's objections and to insert the heading "Brief Description of the Drawings" on page 4, line 8 of the specification.

Figure 3 have been amended to conform to the Figure 3 as originally filed. Figure 1 as pending in the application is consistent with Figure 1 as originally filed. The amendments to the figures are consistent with the figures last entered on September 2006.

No new matter is believed to have been introduced. Applicants respectfully request that if there should be any questions regarding the foregoing amendments or remarks that the Examiner call the undersigned.

I. OBJECTION TO THE SPECIFICATION AND FIGURES

The substitute specification filed March 8, 2007 has been entered. There are no previous objections to the substitute specification remaining and there is no new matter rejection to the substitute specification.

The specification has been objected to for lacking a heading "Brief Description of the Drawings". The specification has been amended to insert the heading. Accordingly, the objection may be properly withdrawn.

II. OBJECTION TO THE CLAIMS

Claims 31, 32 and 33 stand objected to for setting forth parentheses around the sequence identification numbers in the claims. Applicants have amended the claims to remove the parentheses. Accordingly, the objection may be properly withdrawn.

III. REJECTION UNDER 35 U.S.C. §112, SECOND PARAGRAPH

Claims 31-33 and 37 stand rejected under 35 U.S.C. §112, second paragraph as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, the Office

Action alleges that it is not clear what the use of the parenthetical marks around the sequence identifiers are intended to indicate. Applicants have removed the parentheticals around the sequence identifiers. The rejection may be properly withdrawn.

IV. REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 32, 35, 37 and 38 stand rejected under 35 U.S.C. §112, first paragraph as allegedly failing to comply with the written description requirement with respect to claim language "an epitope portion thereof" of the first 153 residues of SEQ ID NO:38. Applicants respectfully traverse this rejection.

Claim 32 recites an isolated DNA encoding a polypeptide having the first 153 amino acids of SEQ ID NO:38 or an epitope effective portion thereof. Thus, what is being claimed is a DNA encoding the first 153 amino acids or fraction thereof of the 5' terminal end of LSA-1.

Throughout the specification B and T epitopes are described. For instance at page 4 of the specification the following is stated:

> The invention relates more particularly to molecules or to peptide or polypeptide compositions characterized by the presence in their structure of one or more peptide sequences bearing all or part of one or more T epitopes(s) (epitopes implicated in the stimulation of T lymphocytes) and, optionally other epitopes, in particular B epitopes (epitopes corresponding to the antibodies produced by B lymphocytes) characteristic of the proteins resulting form the infectious activity of *P. falciparum* in the liver cells.

At page 11 of the specification the following is stated:

> The invention also relates to any molecule or polypeptide composition comprising at least one peptide sequence bearing all or part of one or more epitopes characteristic of a protein produced in the hepatocytes infected by *P. falciparum* and bearing more particularly all or part of one or more T epitope(s) of the proteins produced at the hepatic stage of *P. falciparum* characterized in that this peptide sequence comprises successively:
>
> -all or part of the sequence of the first 153 amino acids shown in figure 7, . . .

At page 25 the following is stated:

> The molecules according to the invention posses antigenic properties characteristic of the antigens which bear T epitopes and optionally B epitopes, and which are specific for the hepatic stage of the development

> of *P. falciparum* or specific for the sporozoite, hepatic and blood stages simultaneously.

At page 40 of the specification the following is stated:

> The immunization of mice with the LSA-R-NR proteins and the study of the response of lymphocytes of these mice, as well as the immunization with the LSA-R peptides of mice of different haplotypes with peptides LSA-R, LSA-J and LSA-NR and finally the study of the responses of lymphocytes of the subjects exposed to malaria towards the LSA-R peptides had shown that a T epitope for man and the mouse is not defined by the repetitive part of the LSA molecule. More detailed studies show the existence of a T epitope in the LSA-R peptides.

At page 41 it is explained that a T epitope of the LSA molecule is defined by LSA-NR and that two other T epitopes are contained in sequences of the synthetic LSA-J and LSA-R in subjects from Madagascar and Senegal. At page 41, the specification reveals:

> The identification of those epitopes capable of stimulating the T lymphocytes is of great importance in as much as it has been established in the malaria of rodents that the production induced by irradiated sporozoites is dependent on the production of lymphocytes cytotoxic for the infected hepatocyte, and capable of destroying them.

Page 42 of the specification goes on to discuss the results of T epitopes found during experiments with chimpanzees and concludes that:

> Sixty percent of the proliferating lymphocytes are of the CD8+ phenotype, which corresponds in particular to cytotoxic T lymphocytes.

At page 43 of the specification it is explained that further investigation using a cytolysis test revealed that:

> These results demonstrate that the T epitopes, defined above, are capable of activating the cytolytic T lymphocytes specific for the polypeptide sequences in question.

At page 44 of the specification the antigenic and/or immunogenic properties of the polypeptides of the invention are described. Thus, the recombinant complete protein 536 "induces the function of antibodies (presence of B epitopes) and induces proliferative responses of lymphocytes (presence of T epitope) in the chimpanzee and in man."

It is revealed that some of the peptides disclosed in the present invention "bear additionally major T epitopes and B epitopes."

Thus, the specification clearly describes that the peptides of the invention have T and B cell epitopes and that the T cell epitopes are not found in the repetitive part of LSA-1 and are found in the first 153 amino acids of Figure 7 (SEQ ID NO:38). The repetitive portions of 17 amino acids are described in the specification and can be seen from Figure 7 that these repetitive sequences begin with amino acid residue 192.

Moreover, in the analysis of the written description requirement the issue is whether a person skilled in the art at the time of filing of the present application would recognize that the inventors had possession of the claimed invention. To satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and that the invention, in that context, is whatever is now claimed. *Vas Cath, Inc. v. Mahurkar,* 935 F.2d 1555, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). In fact, the written description requirement can even be met if the claimed invention is merely "inherent" in the disclosure. *Kennecott Corp. v. Kyocera International, Inc.*, 835 F.2d 1419, 5 USPQ2d 1194 (Fed. Cir. 1987).

Applicants set forth in the specification the sequence of the polypeptide encoded by the DNA now being claimed and more particularly described the first 153 amino acids of the polypeptide bearing T cell epitopes. It was also known at the time the invention was made that minimal epitope sizes for most antigenic moieties comprised 5 and 20 amino acids in length. When Applicants described the T cell epitopes found in the N-terminal domain of the LSA-1 polypeptide, one of skill in the art would understand and be capable of identifying sequences of 5-20 amino acids that can provide useful epitopes. Such was described by Applicants in the specification and convey to one of skill in the art that portions, fragments, and the full 153 amino acid length of the N-terminal domain of the LSA-1 polypeptide convey T cell epitopes. Such was conveyed and contemplated by Applicants at the time of filing. The Examiner is again directed to page 11, which states:

> The invention also relates to any molecule or polypeptide composition comprising at least one peptide sequence bearing all or part of one or more epitopes characteristic of a protein produced in the hepatocytes infected by *P. falciparum* and bearing more particularly all or part of one or more T epitope(s) of the proteins produced at the hepatic stage of *P. falciparum* characterized in that this peptide sequence comprises successively:

-all or part of the sequence of the first 153 amino acids shown in figure 7, . . .

Prior to the filing of the present invention it was known in the art that T cell antigenic sites are amphipathic structures and bind in the MHC groove with a hydrophobic side facing the MHC molecules, which the hydrophilic side reacts with the T cell receptor. It was also known that peptides binding to class I MHC molecules are from 8 to 10 amino acids in length while those that bind to MHC II are longer; e.g., 8 to greater than 20 amino acids. Also known were methods for determining T epitopes from the amino acid sequences of proteins (Annex 1).

Besides the amphipathic nature of T epitopes, it was known that there was a sequence pattern common to T cell epitopes, known as the Rothbard motif as evidenced in Annex II. Predication of T cell antigenic sites from using algorithms such as the AMPHI algorithm was also available to the skilled artisan prior to the filing date of the present invention, (Annex III and Annex IV).

Thus, Applicants submit that the skilled artisan would appreciate that the inventors did in fact have possession of the claimed invention. In view of the foregoing remarks, Applicants respectfully request withdrawal of this rejection.

VI. REJECTION UNDER 35 U.S.C. §102(b)

Claims 32 and 38 stand rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Guerin-Marchand et al. (Nature 329: 164-67). Applicants respectfully traverse this rejection.

Guerin-Marchand et al. disclose a molecule expressed specifically during the hepatic phase, which was identified by screening a library of genomic DNA clones in an expression vector with polyclonal sera. This molecule is a Liver Stage Specific Antigen from clone DG307 and consists of 17 repetitive amino acids, which are representative by the formula:

*EQQSDL*EQERLAKEKLQ

and are underlined in Figure 4.

The Examiner purports that the "claims read on any DNA sequence encoding an epitope effective portion of residues 1-513 of SEQ ID NO:38 and a B-cell epitope of the liver stage antigen." Applicants respectfully submit that this is not correct.

Claim 32 recites an isolated DNA encoding a polypeptide comprising at least one epitope of LSA-1 wherein the polypeptide *consists of the first 153 amino acids* of the amino acid sequence of SEQ ID NO:38 or an epitope effective portion thereof. The claims thus do not include residues 1-513 as proposed by the Examiner but are portions thereof. There is no sequence of EQQSDL in the first 153 amino acids of SEQ ID NO:38 as described by the cited reference. Rather this sequence can be found after amino acid 191 in SEQ ID NO:38. Thus, Guerin-Marchand et al. do not teach the epitope compositions of the claimed invention but rather teaches a sequence C-terminal to the region of the claimed invention. Accordingly, the rejection may be properly withdrawn.

Claims 32 and 38 stand rejected under 35 U.S.C. §102(b) as allegedly anticipated by U.S. Patent No. 5,602,031. Applicants respectfully traverse this rejection.

U.S. Patent No. 5,602,031 relates to an isolated or purified nucleotide sequence encoding a polypeptide produced in hepatocytes infected by *P. falciparum* comprising the sequence:

Leu-Ala-Lys-Glu-Lys-Leu-Gln-X-Gln-Gln-Ser-Asp-Leu-Glu-Gln-Glu-Arg, in which X is Glu or Gly.

The foregoing sequence taught by U.S. Patent No. 5,602,031 is not found in the first 153 amino acids of SEQ ID NO:38 as set forth by Applicants' claimed invention. Rather the sequence taught by U.S. Patent No. 5,602,031 is found following amino acid 191 of SEQ ID NO:38. Thus, the cited reference does not teach Applicants' claimed invention and accordingly cannot anticipate Applicants' invention. Applicants respectfully request withdrawal of this rejection.

Claims 32 stands rejected under 35 U.S.C. §102(b) as allegedly being anticipated by WO 88/05785. Applicants respectfully traverse this rejection.

WO 88/05785, whose U.S. counterpart is U.S. Patent No. 5,599,542 is a divisional of U.S. Patent No. 5,602,031 (which is addressed above).

WO 88/05785 relates to an isolated or purified nucleotide sequence encoding a polypeptide produced in hepatocytes infected by *P. falciparum* comprising the sequence:

Leu-Ala-Lys-Glu-Lys-Leu-Gln-*X-Gln-Gln-Ser-Asp-Leu*-Glu-Gln-Glu-Arg, in which X is Glu or Gly (i.e., containing the sequence EQQSDL).

The foregoing sequence taught by WO 88/05785 is not found in the first 153 amino acids of SEQ ID NO:38 as set forth by Applicants' claimed invention. Rather the sequence taught by WO 88/05785 is found following amino acid 191 of SEQ ID NO:38. Thus, the cited reference does not teach Applicants' claimed invention and accordingly cannot anticipate Applicants' invention. Applicants respectfully request withdrawal of this rejection.

VI. REJECTION UNDER 35 U.S.C. §103

Claims 32 and 37 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over WO 88/05785. Applicants respectfully traverse this rejection.

As stated above, WO 88/05785 as set forth in the translated U.S. counterpart, U.S. Patent 5,599,542 and 5,602,031, describes a 17 amino acid sequence derived from the repeat units from *P. Falciparum* liver stage antigen. This sequence was derived from a DG307 clone and is only a partial sequence of this liver stage antigen, which sequence commences at amino acid 191 of SEQ ID NO:38. There is simply no disclosure of the N-terminal sequence of LSA-1 in WO 88/05785. Applicants recite the N-terminal portion of LSA-1, which is neither taught nor suggested by WO 88/05785.

For example the presently claimed invention is directed to the first 153 amino acids of LSA-1 or an epitope effective portion thereof. Thus, the claimed invention is directed to the N-terminal sequence, which sequence contains T epitopes. This sequence has a particular structure which is not disclosed in WO 88/05785.

The cited reference of WO 88/05785 does not teach or suggest each and every element of Applicants' claimed invention and thus cannot render the claimed invention obvious. Accordingly, Applicants respectfully request withdrawal of this rejection.

VII. REJECTION UNDER OBVIOUS-TYPE DOUBLE PATENTING

Claims 32 and 38 stand rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1 to 6 of U.S. Patent No. 5, 602,031. Applicants respectfully traverse this rejection.

As discussed above, U.S. Patent No. 5,602,031 describes a C-terminal portion of LSA-1 following amino acid residue 191. U.S. Patent No. 5,602,031 recites in claim 1 an isolated or purified nucleotide sequence encoding a polypeptide produced in hepatocytes infected by *P. falciparum* comprising the sequence:

Lew-Ala-Lys-Glu-Lys-Leu-Gln-X-Gln-Gln-Ser-Asp-Leu-Glu-Gln-Glu-Arg, in which X is Glu or Gly.

Claim 2 recites specific variations of the above-sequence, and claims 3 to 5 recite more than one of the sequences in claim 1 or at least one multiple of the sequence of claim 1. Claim 6 recites a vector having one of the DNA molecules and claim 7 recites host cells having the vector of claim 6.

Applicants submit that the present claim 32 is directed to the first 153 amino acids and their epitope effective portions thereof. There is no sequence corresponding to Applicants' claimed invention described by U.S. Patent No. 5,602,031. Under obviousness, a cited reference much teach or suggest each and every element of the claimed invention. Here, the cited reference of U.S. Patent No. 5,602,031, does not teach or suggest an epitope comprising the N-terminal portion before residue number 191. Thus, Applicants' claimed invention is neither taught or suggested by U.S. Patent No. 5,602,031. The reference fails to teach nor suggest the N-terminal domain. Accordingly, Applicants respectfully request withdrawal of this rejection.

Claims 32, 37 and 38 have been rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claim 2 or U.S. Patent No. 5,602,031. Applicants respectfully traverse this rejection.

For the same reasons as stated above with respect to the obviousness-type double patenting rejection, which arguments are incorporated herein by reference, claims 32, 37 and 38 are not obvious over the sequence described in claim 2. The sequence taught by the cited reference start at amino acid 191 of SEQ ID NO:38. Applicants' claimed invention recites a sequence from amino acid 1 to amino acid 153 of SEQ ID NO:38, which sequence is not disclosed nor suggested in this patent.

Accordingly, Applicants respectfully request withdrawal of the rejection.

For at least the foregoing reasons Applicants submit that the claims are patentable and request favorable action. If there remain any questions, the Examiner is respectfully request to call the undersigned. The Commissioner is hereby authorized to charge any fee deficiency or credit any overpayment of fees to Deposit Account No. 02-4800.

Respectfully submitted,

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